

Primary lymphedema (clinical classification).

Diagnosis	Frequency ^{22,31,32,39} (% of all primary forms)
<i>Congenital (onset <2 years after birth)</i>	6-12
Familial, autosomal dominant (Nonne-Milroy disease)	
Familial, non-dominant inheritance	
Sporadic (most common congenital form)	
<i>Lymphedema precox (onset between 2-35 years)</i>	77-94
Familial, autosomal recessive (Meige disease)	
Sporadic (83-94% of all lymphedema precox)	
<i>Lymphedema tarda (onset after 35 years of age)</i>	11

FIG. 1A

Title: Use of Lymphangiogenic Agents
To Treat Lymphatic Disorders
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Functional Classification of Primary Lymphedema	
Distal Obliteration (80%)	Proximal Obliteration (10%)
Gender Female	Male or Female
Onset Puberty	Any age
Time Ankle; bilateral	Whole leg, thigh; unilateral
Location Rapid	Rapid
Progression Frequently positive	None
Family history Congenital	Whole leg; unilateral or bilateral
	Progressive
	Frequently positive

FIG. 1B

Secondary lymphedema

Blockade at the level of the lymph node

- Regional lymph node dissection
 - Axillary (post-mastectomy lymphedema)
 - Pelvic and para-aortic (leg and groin lymphedema)
 - Neck (head and neck lymphedema)
- Neoplastic disease
 - Hodgkin lymphoma
 - Metastatic cancer
 - Prostate cancer
 - Cervical cancer
 - Breast cancer
 - Melanoma

Disruption or obliteration of lymphatic channels

- Surgery, e.g. ilio-femoral bypass
 - Direct injury, e.g. trauma of the medial aspect of the thigh
 - Radiation-induced fibrosis
 - Neoplastic infiltration of lymphatic channels
 - Rheumatoid arthritis
 - Filariasis
 - Recurrent infection, e.g. erysipelas
-

FIG. 1C

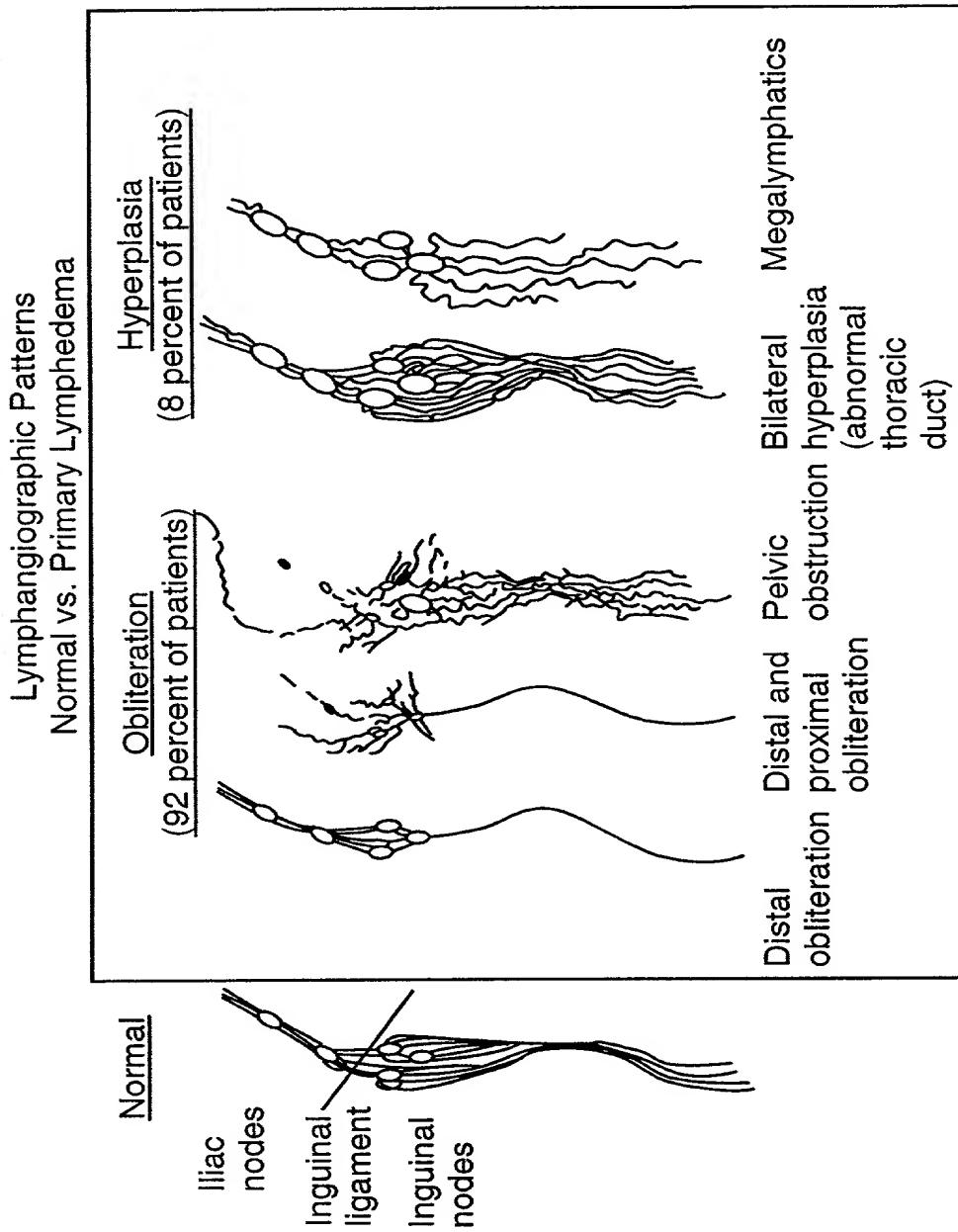


FIG. 2

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Rabbit Ear Lymphedema Model
Clinical Appearance — 5 Month



FIG. 3

VEGF-2

Control

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Rabbit Ear Lymphedema Model
Lymphoscintigraphy — 5 Month Post-Op

VEGF-2

Control

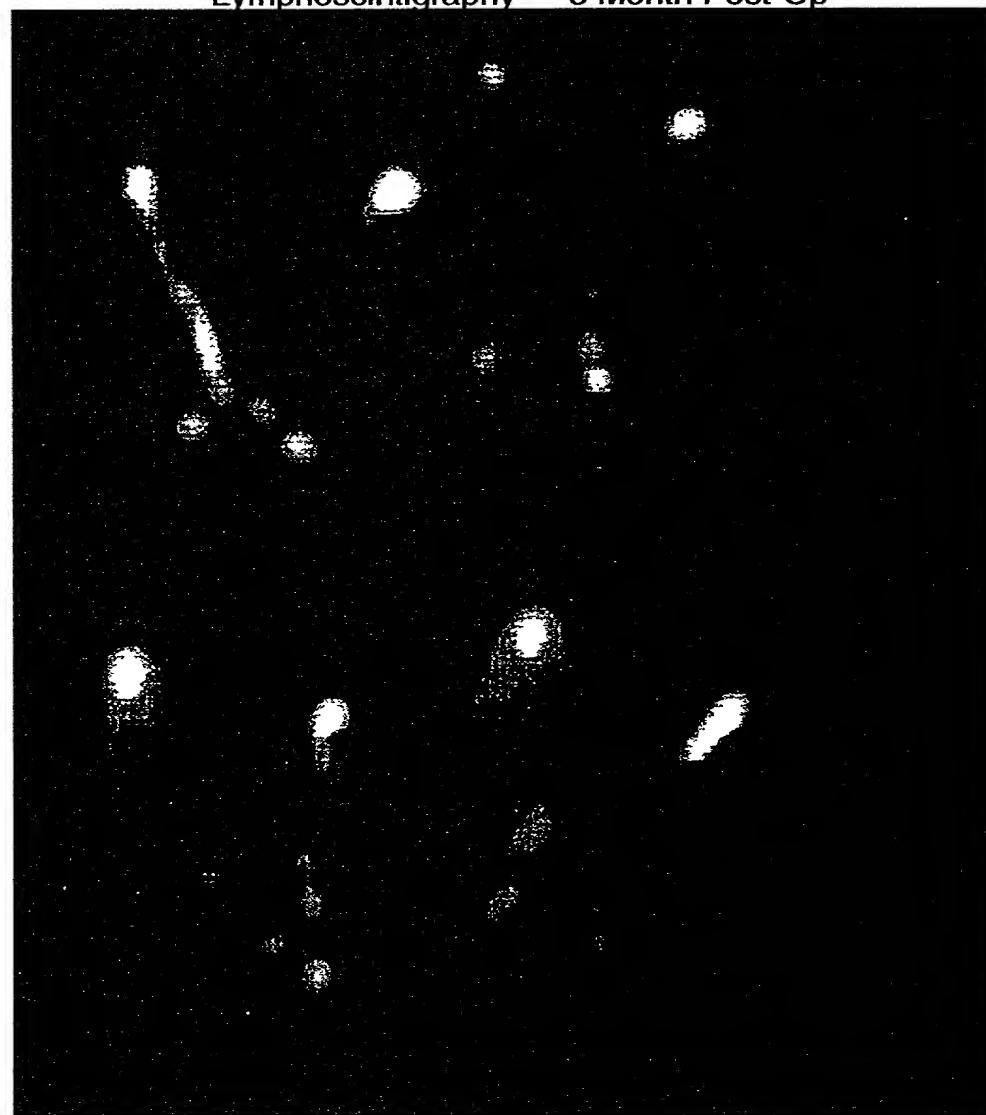
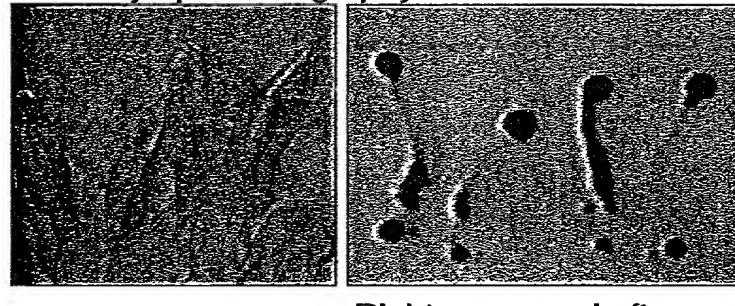


FIG. 4

Rabbit Ear Lymphedema Model
Lymphoscintigraphy — Orientation



Right
Operated Left
Normal

FIG. 5

Rabbit Ear Lymphedema Model
Lymphoscintigraphy — Early Post-Op

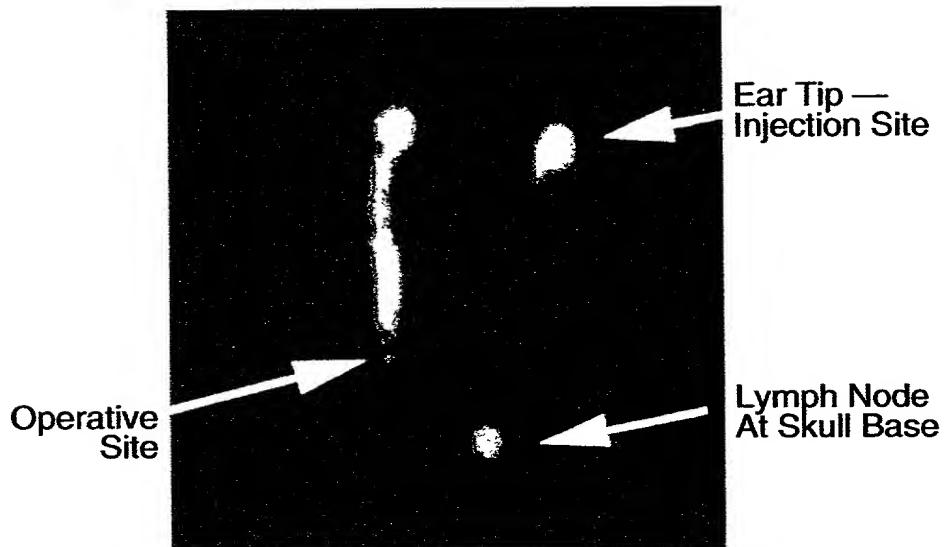


FIG. 6

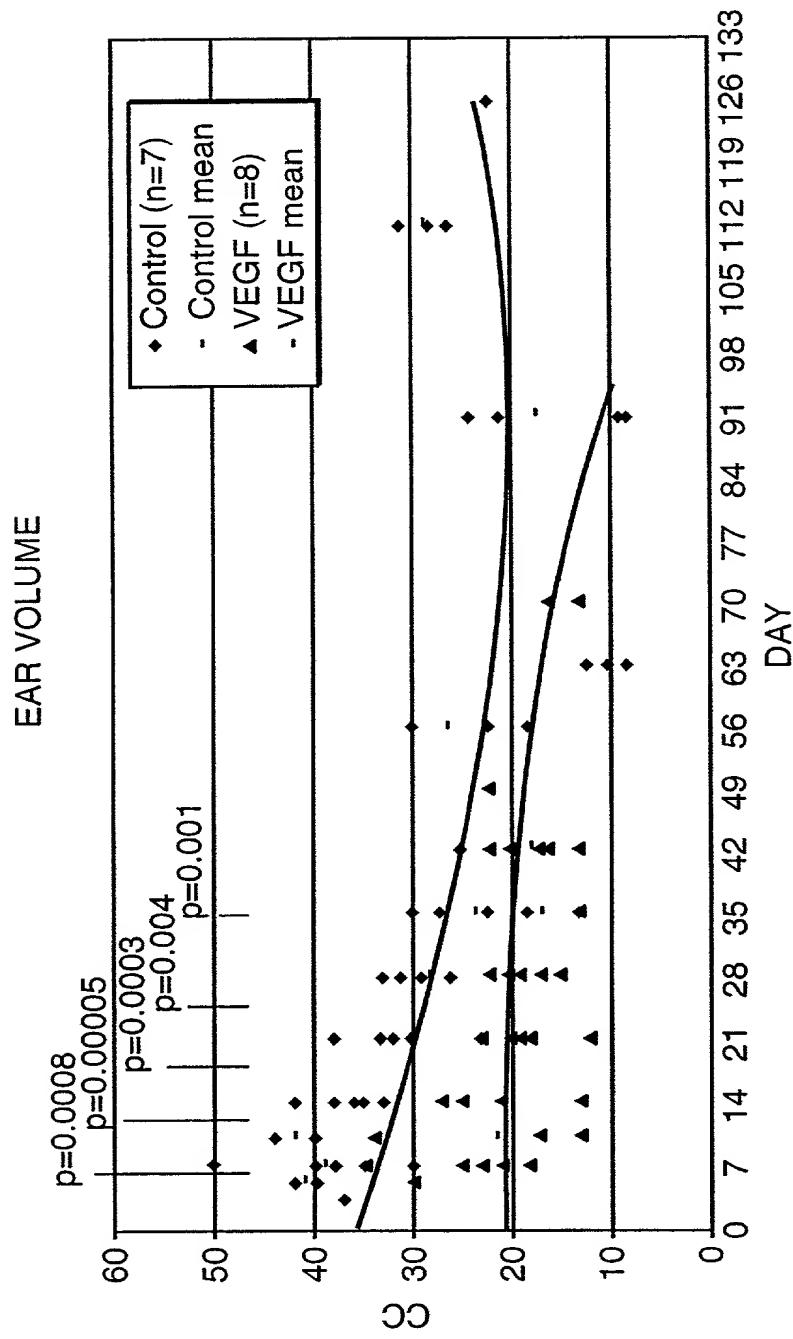


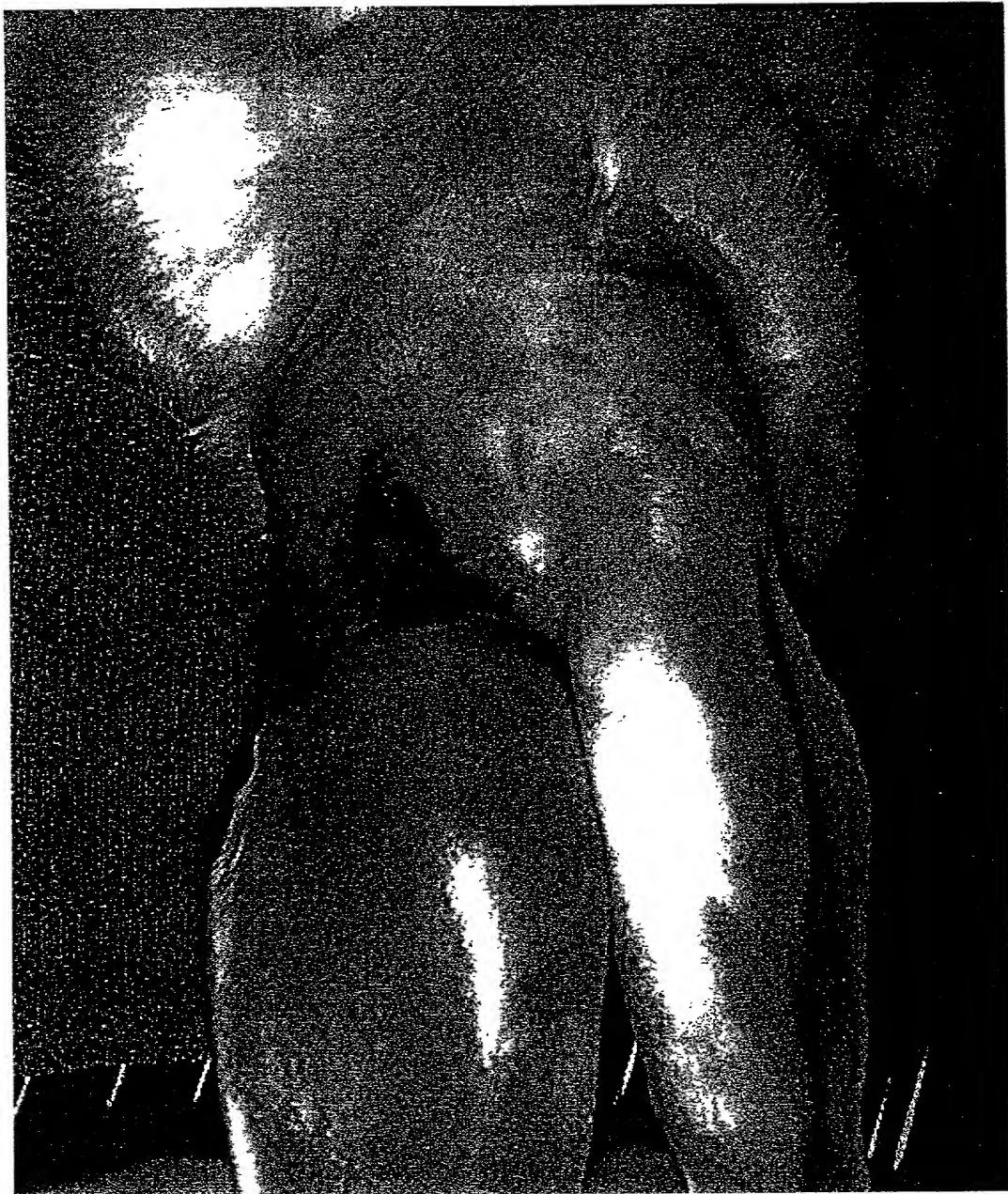
FIG. 7

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FIG. 8

Rabbit Ear Lymphedema Model
3 Days Post-Op



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Human Lymphoscintigraphy
Right Lower Extremity

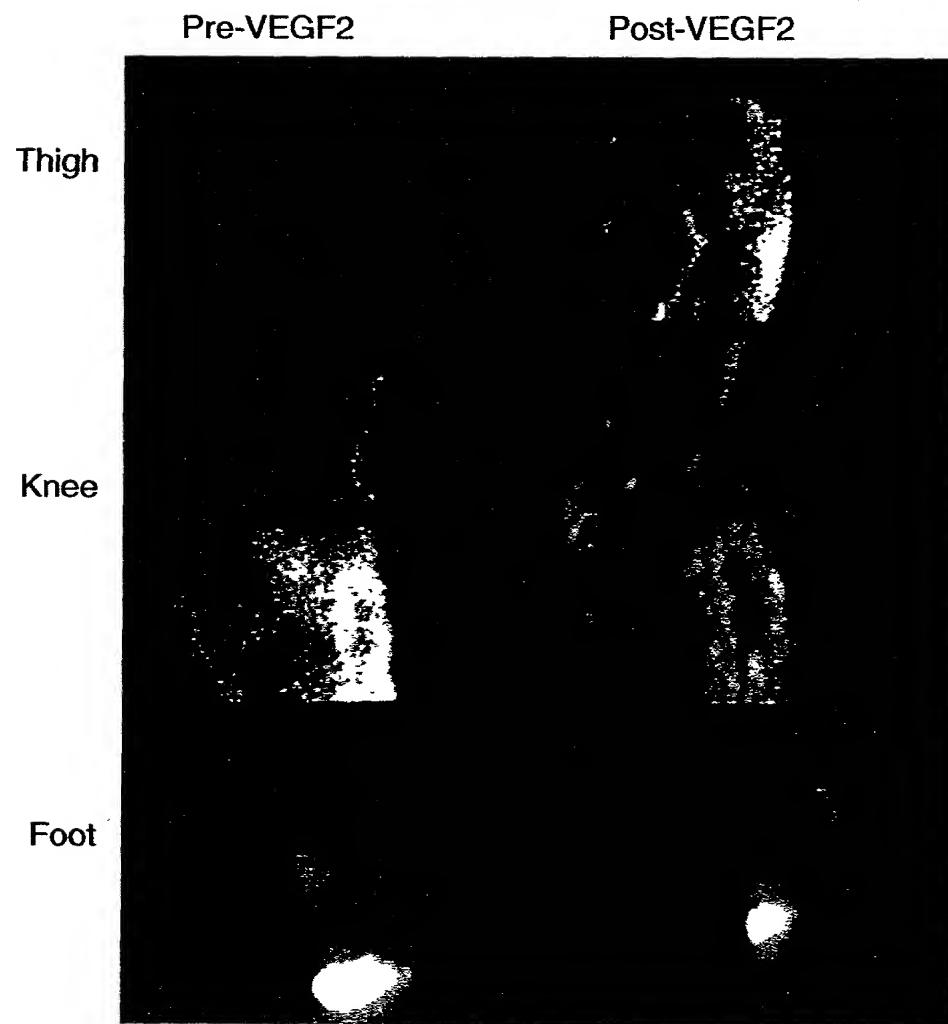


FIG. 9

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Ultrasound Imaging of Intra-Muscular
VEGF-2 Gene Transfer: Lymphedema

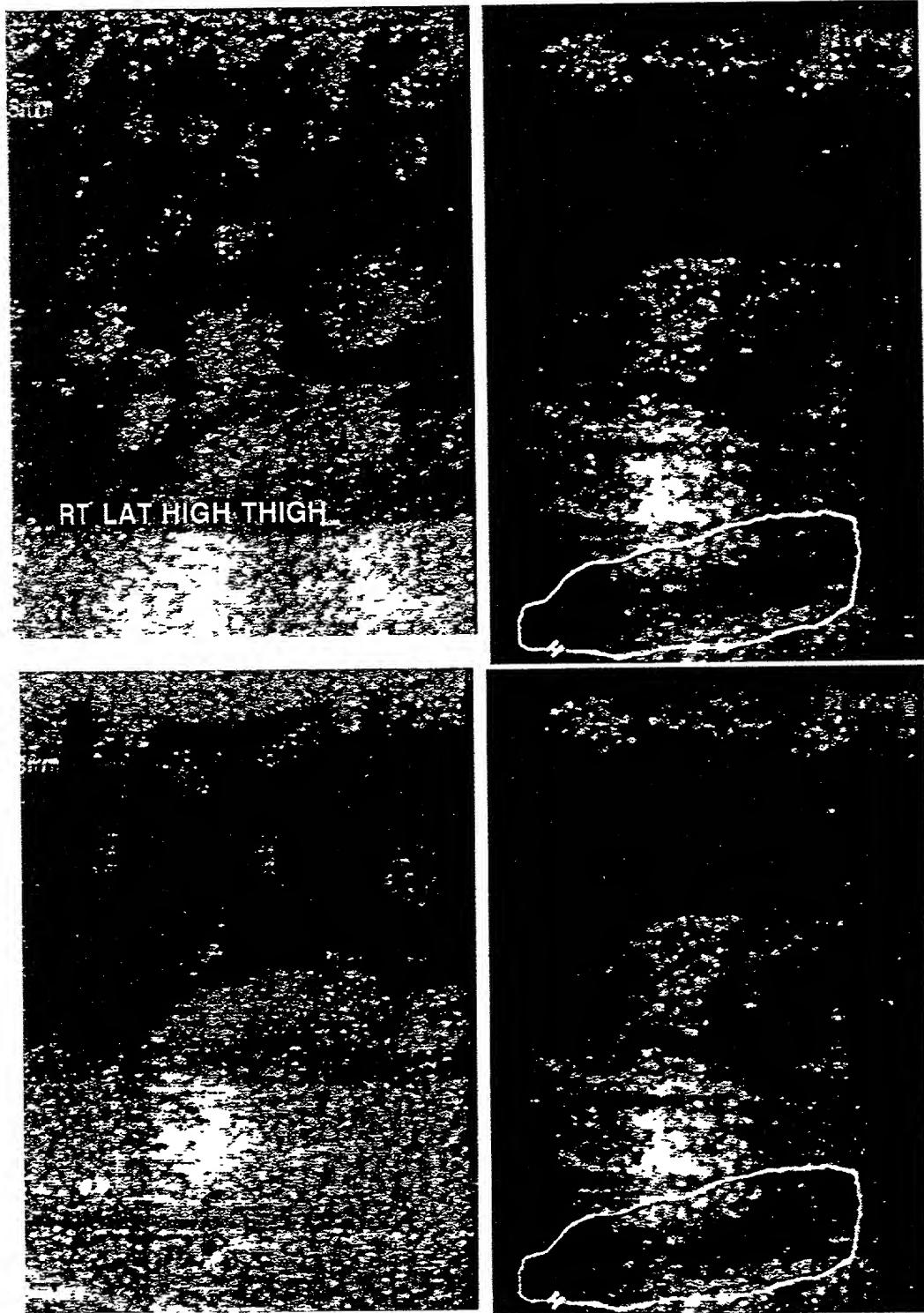


FIG. 10

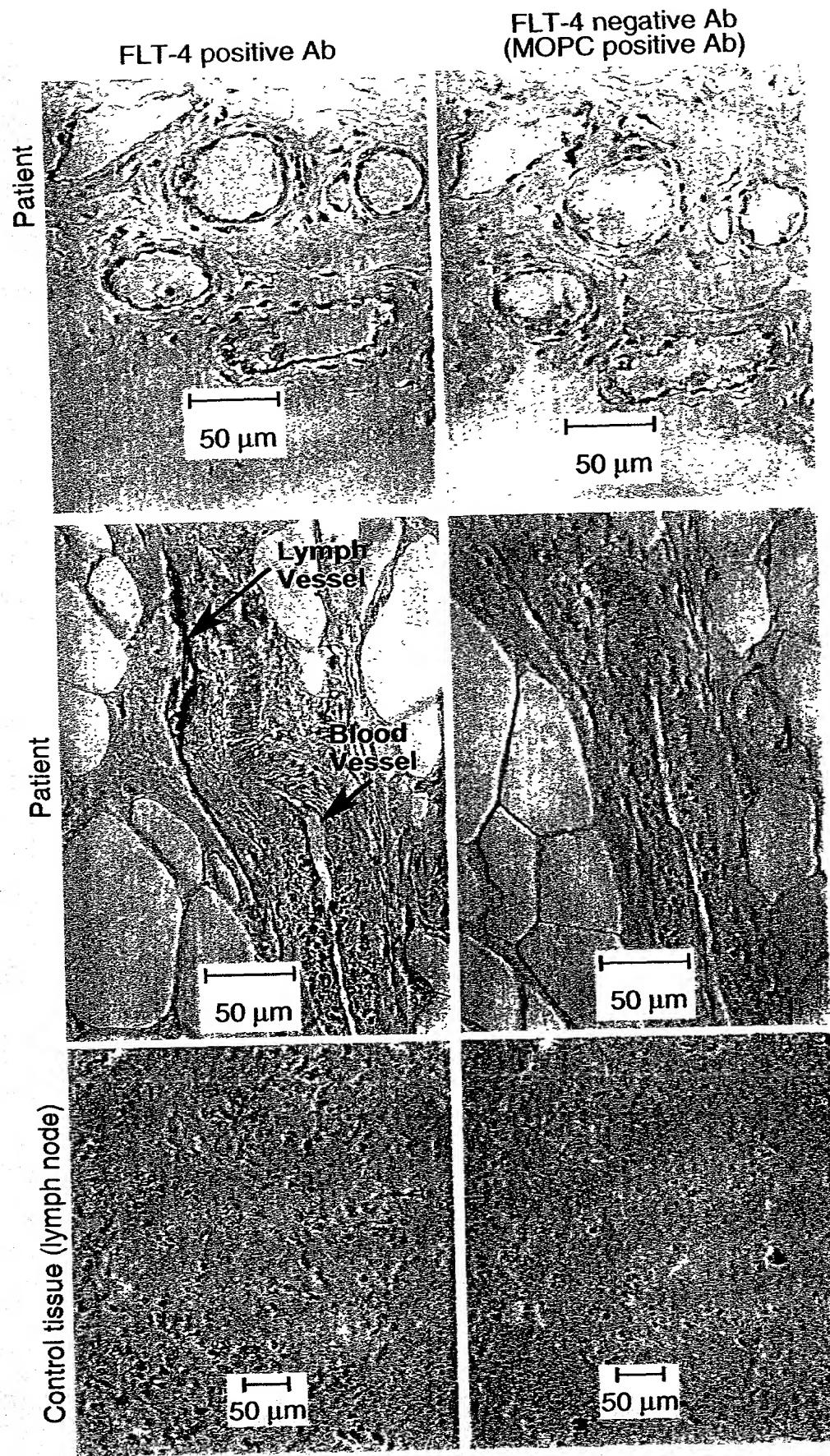


FIG. 11



FIG. 12A



FIG. 12B

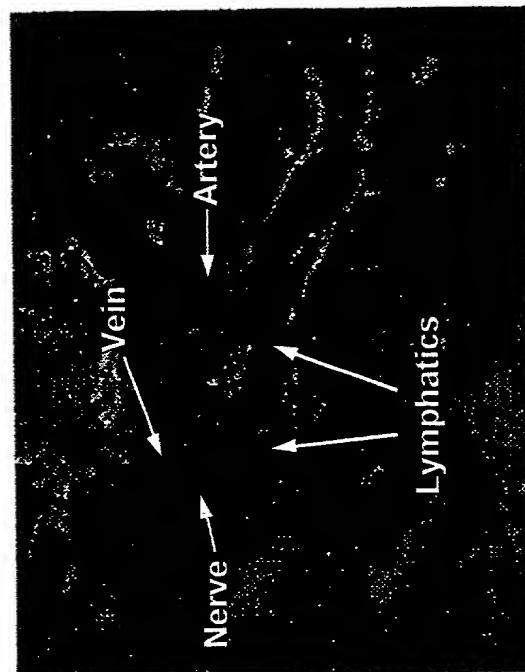


FIG. 12C

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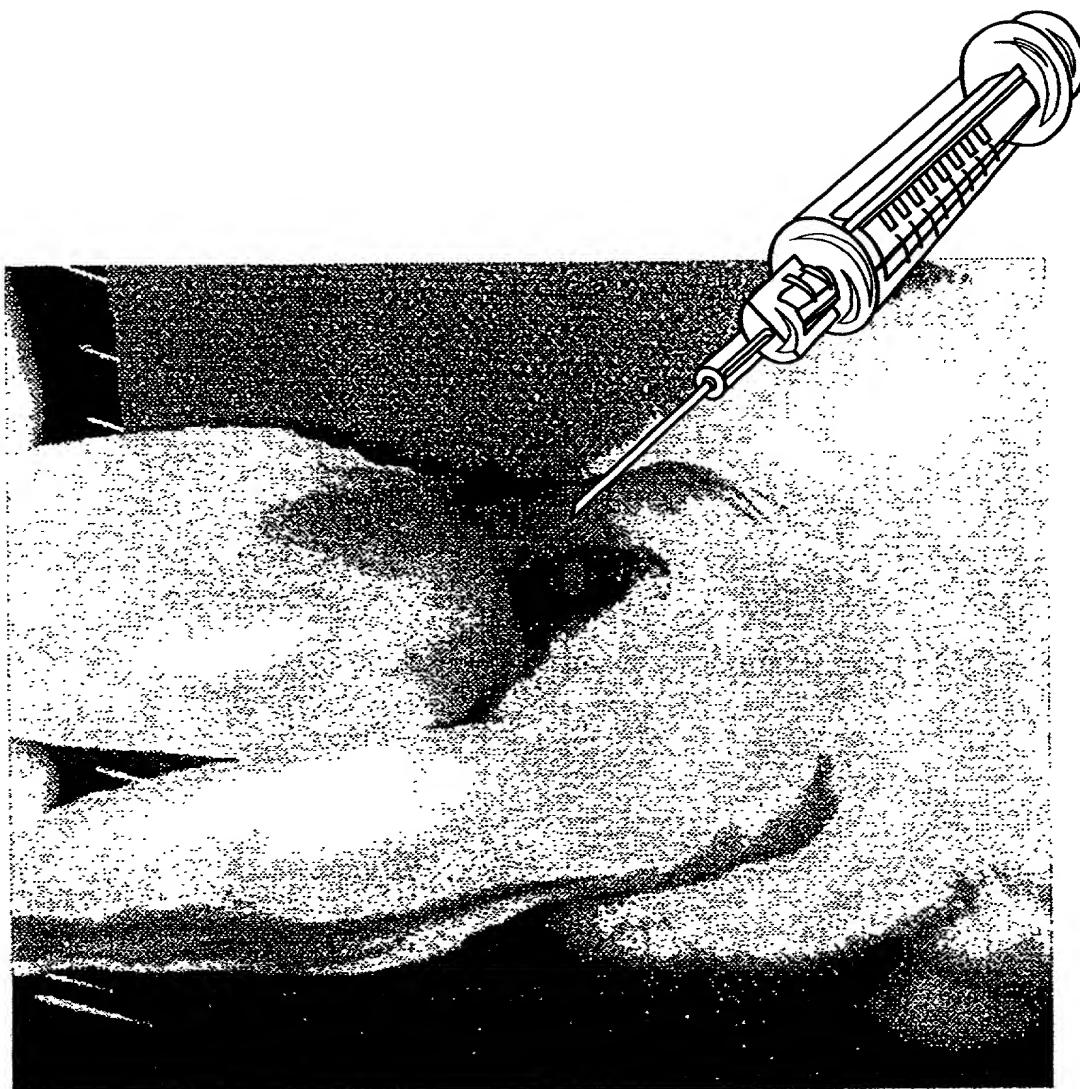


FIG. 13A

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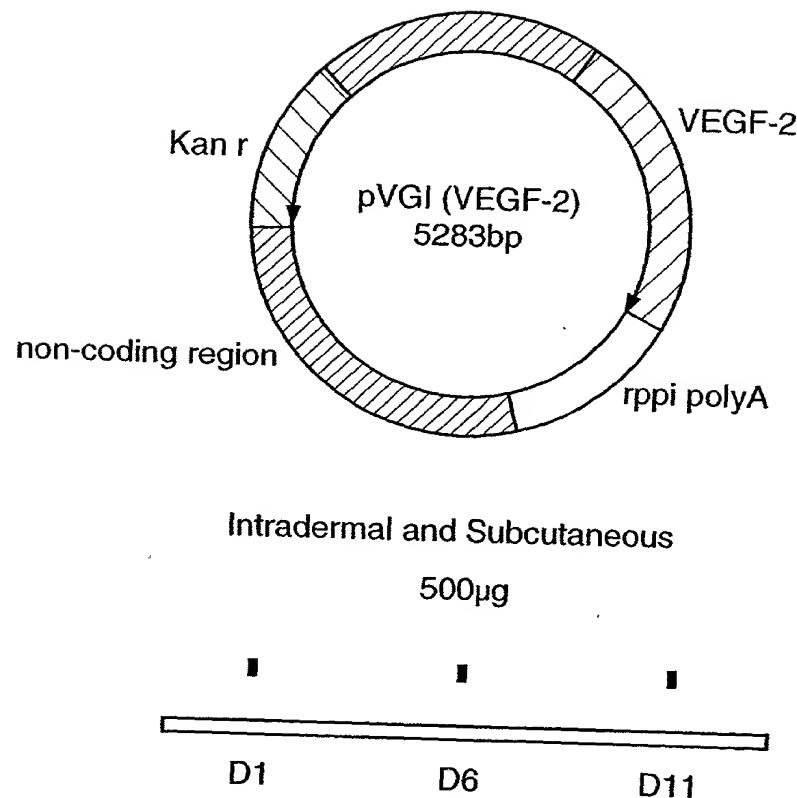


FIG. 13B

Title: Use of Lymphangiogenic Agents
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FIG. 14A

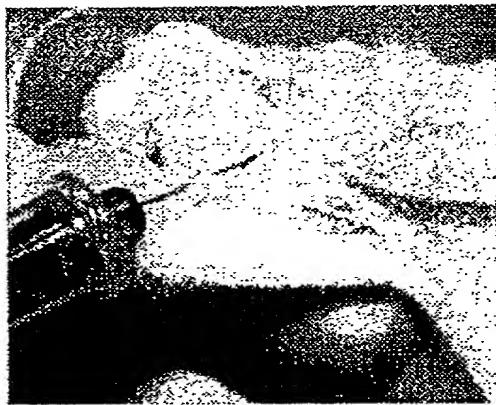


FIG. 14B

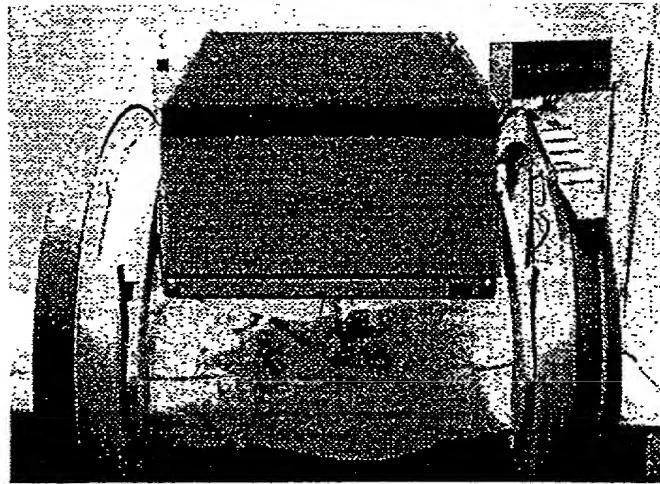
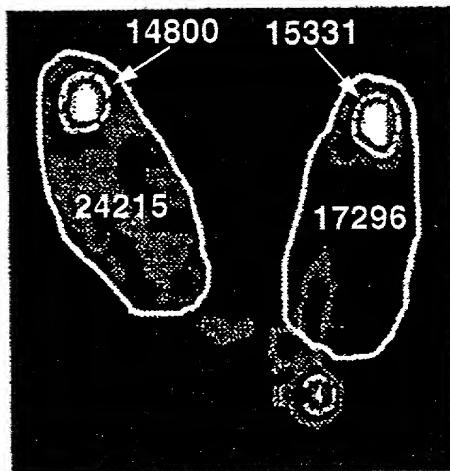
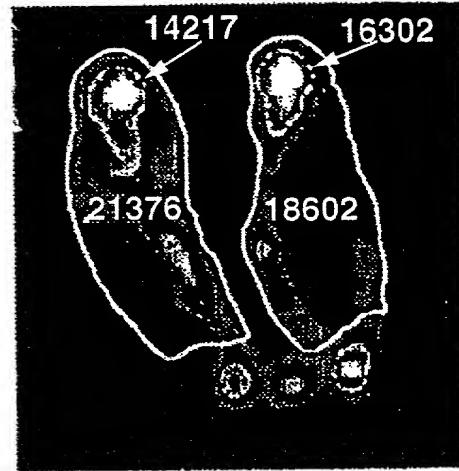


FIG. 14C



$$(24125-14800)/(17296-15331) = 4.75$$

FIG. 15A



$$(21376-14217)/(18602-16302) = 3.11$$

FIG. 15B

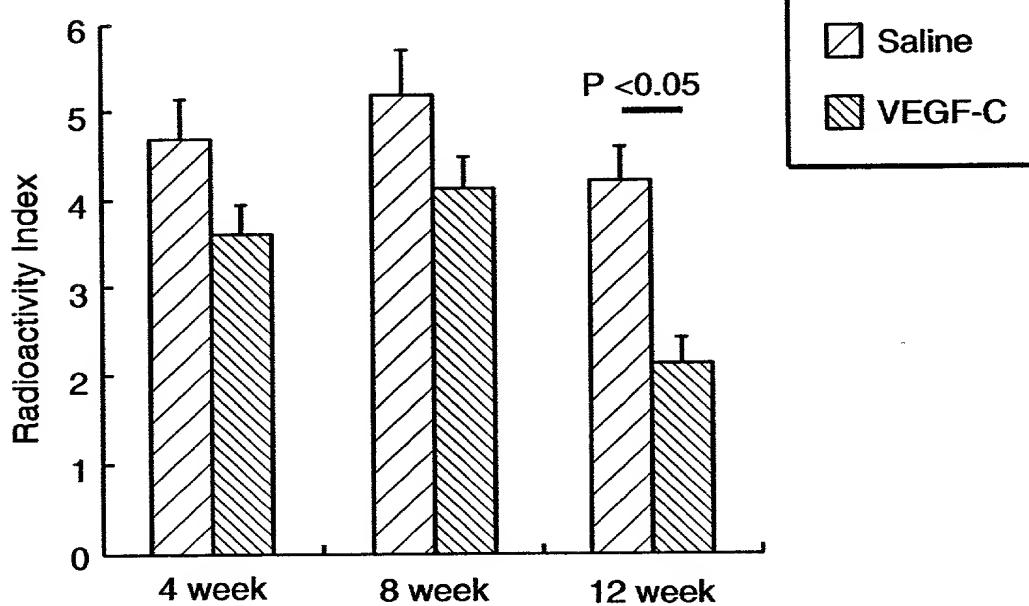


FIG. 15C

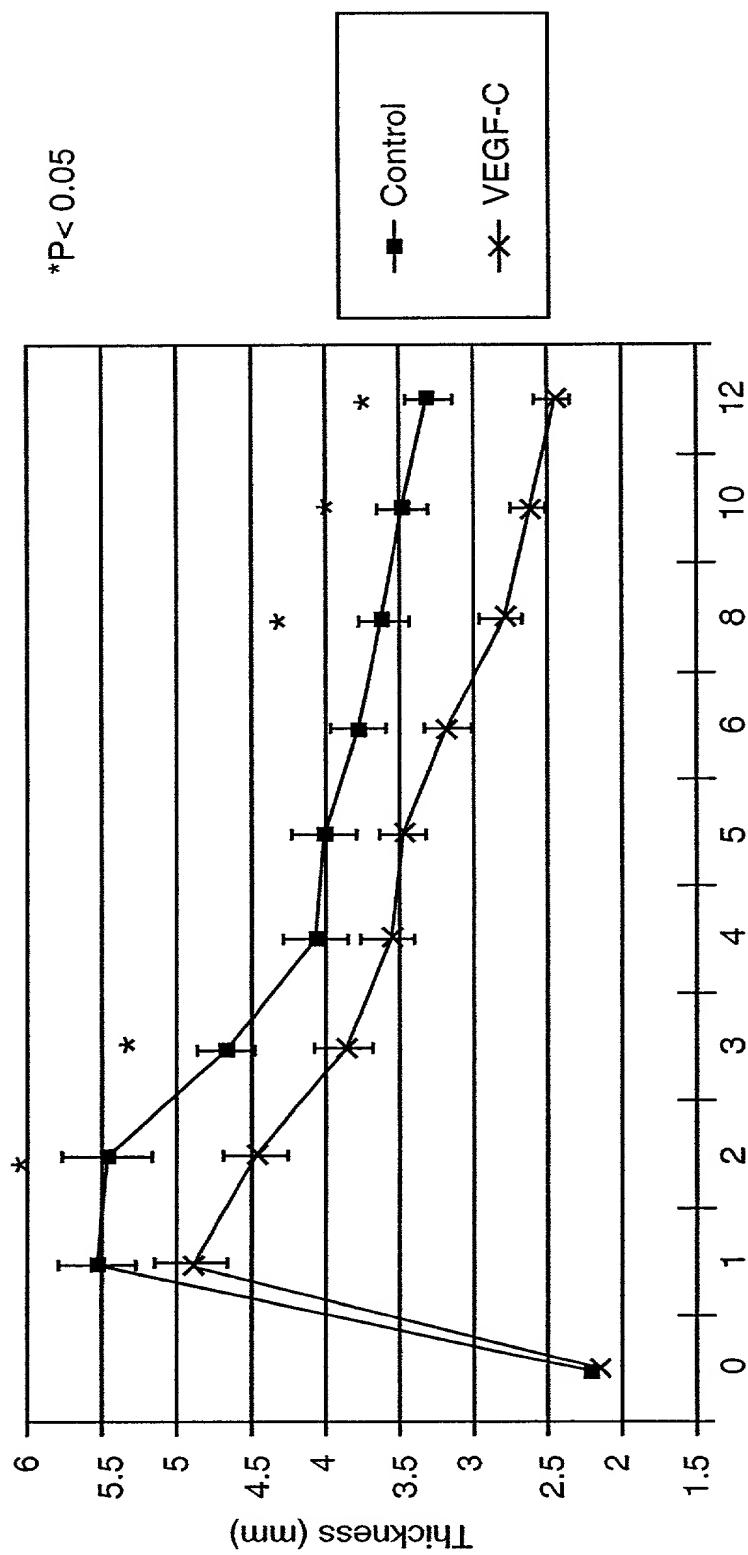


FIG. 16A

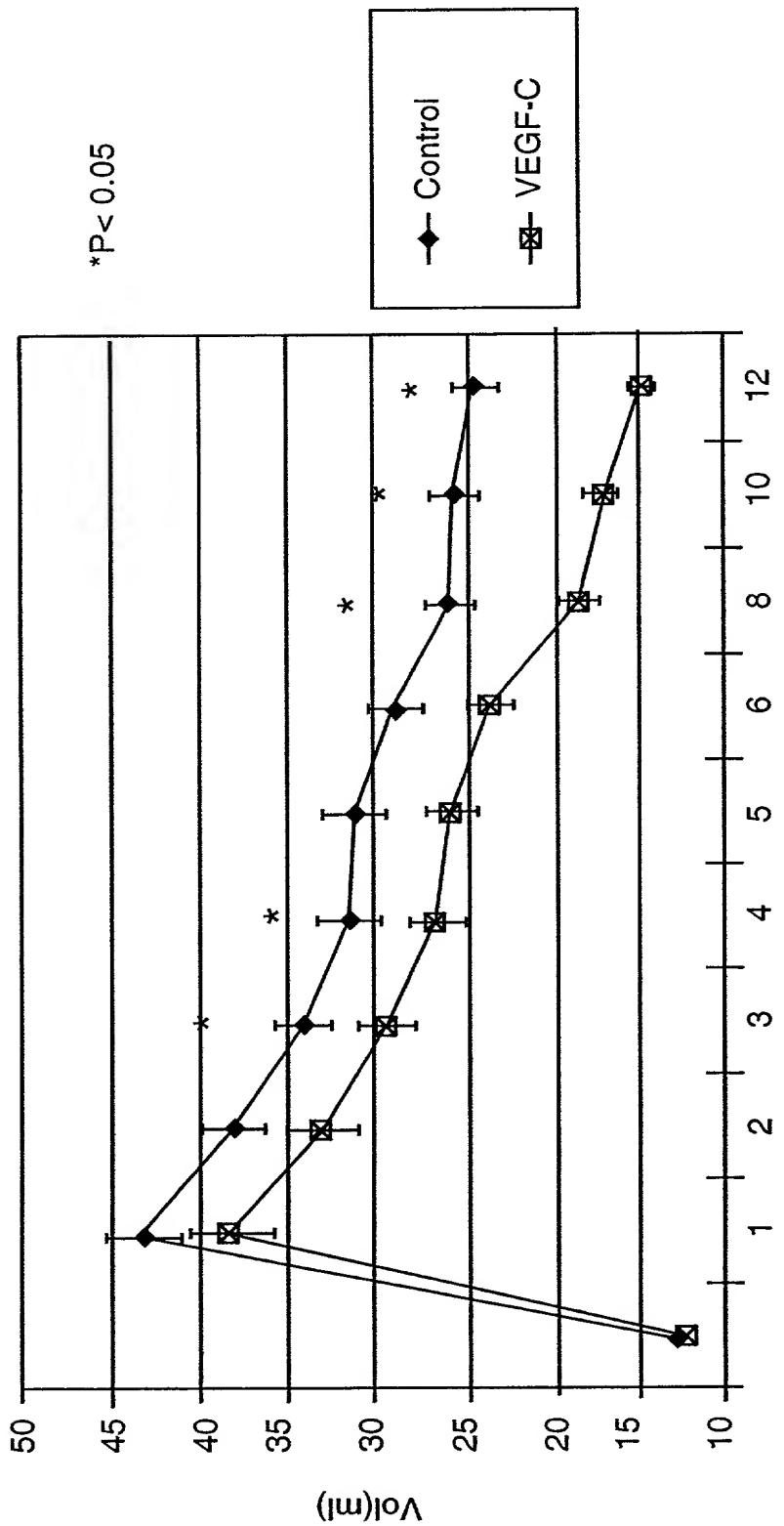
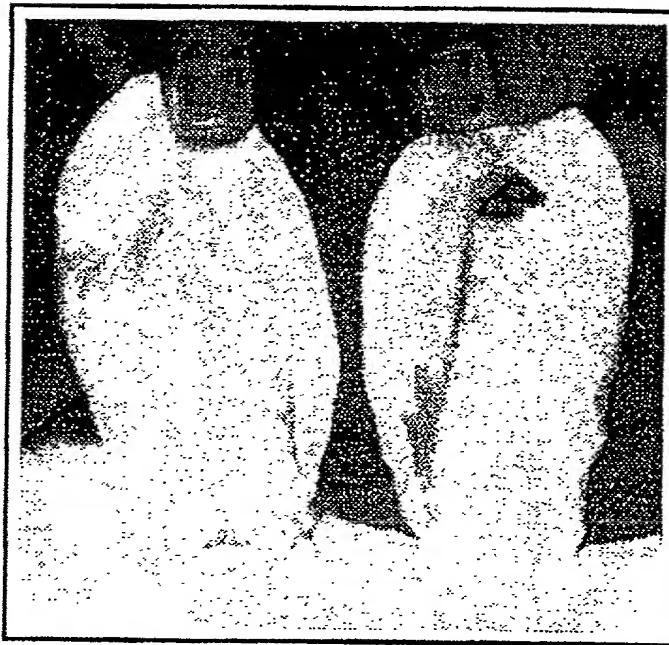


FIG. 16B

FIG. 17A

Control



VEGF-C

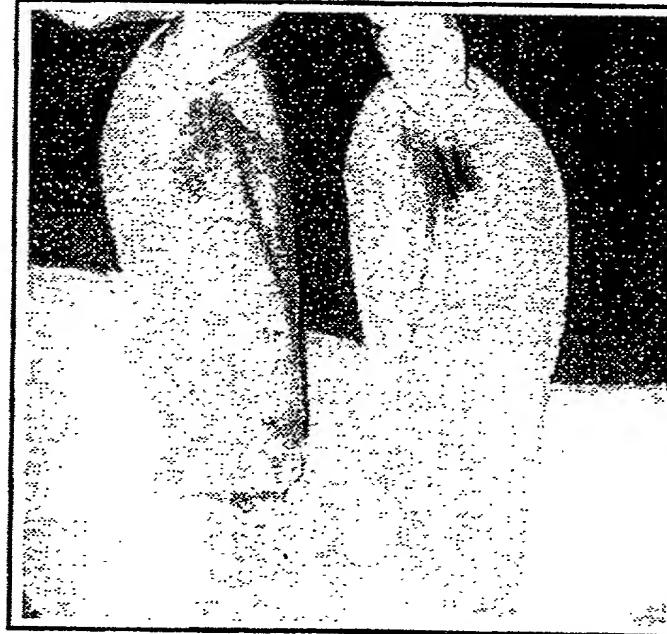
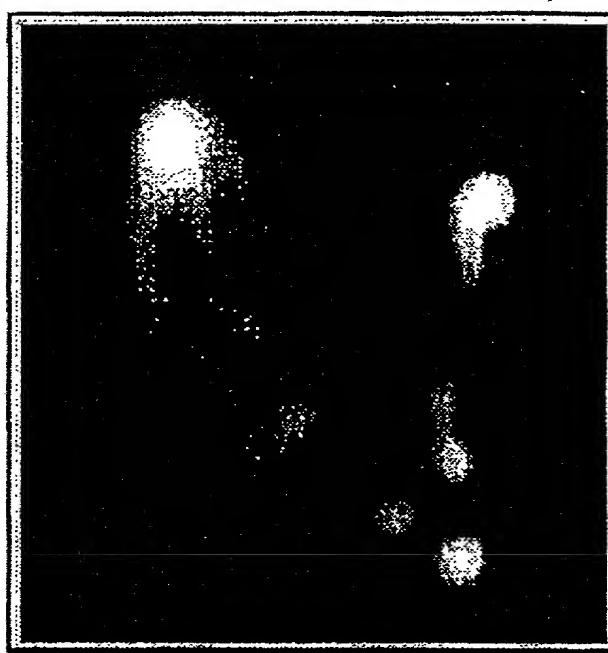


FIG. 17B

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FIG. 17C

Control



VEGF-C

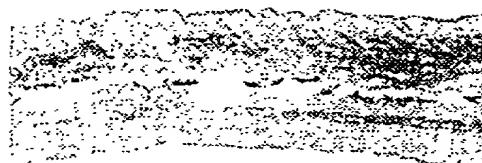


FIG. 17D

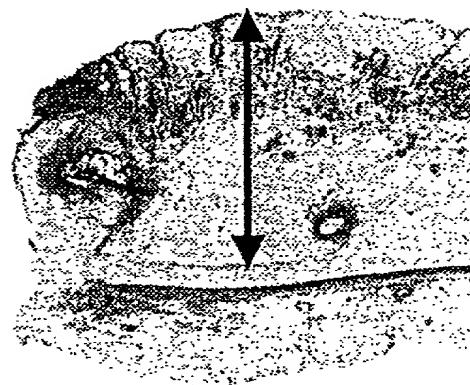
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Normal Ear



LE-Saline



Normal Ear



LE-VEGF-C



FIG. 18A

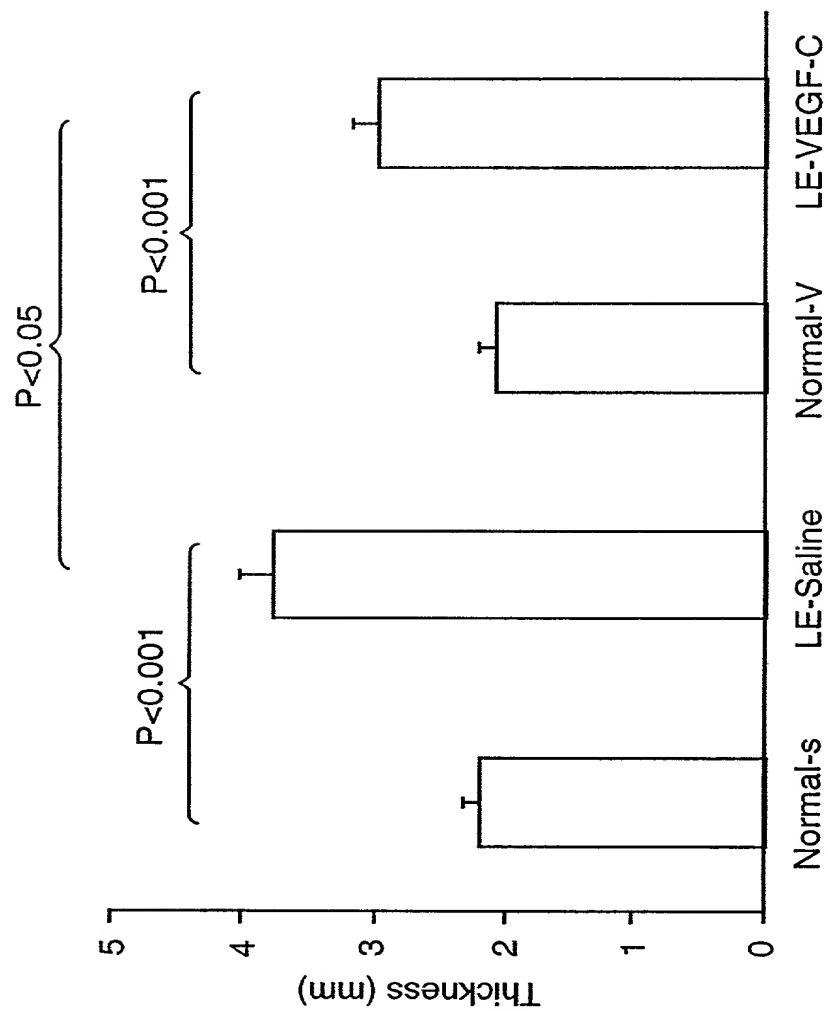


FIG. 18B

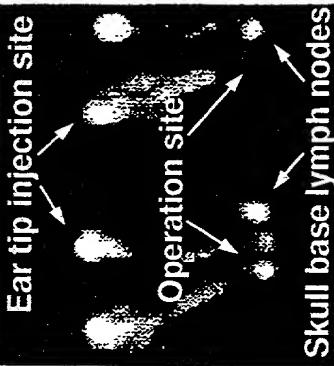


FIG. 19A



FIG. 19B



FIG. 19G
VEGF-C
day 1

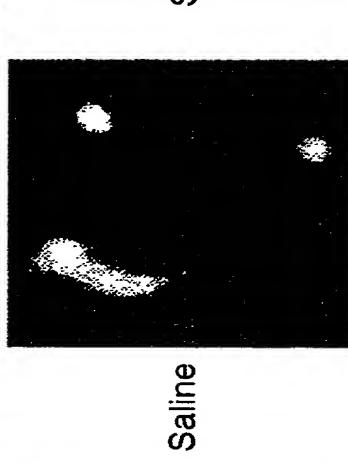


FIG. 19H
VEGF-C
4 week

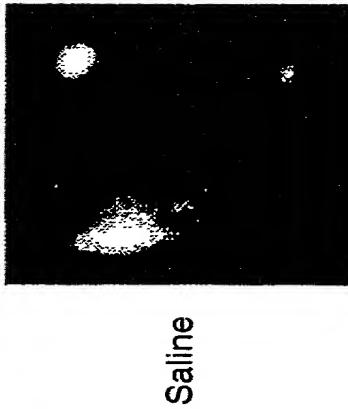


FIG. 19C
VEGF-C
8 week

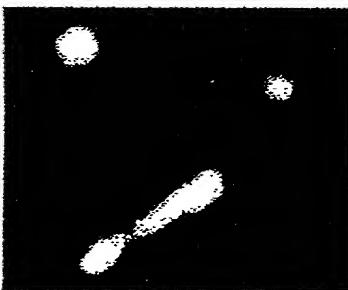


FIG. 19J
VEGF-C
12 week



FIG. 19E
VEGF-C
12 week



FIG. 19F
VEGF-C
12 week



FIG. 19I
VEGF-C
12 week



FIG. 19D
VEGF-C
12 week



FIG. 20A

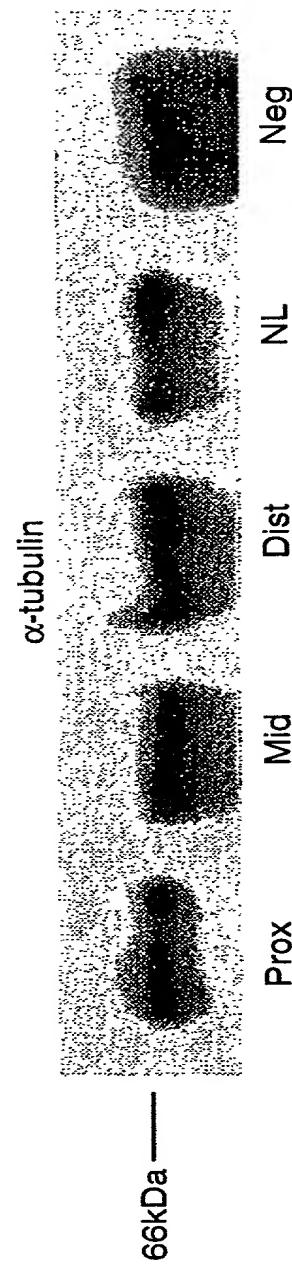


FIG. 20B

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FIG. 21A	
FIG. 21B	

FIG. 21

rb	1	CGGTGGCGG TGGCCGGGC ACACGTGCC AGCATCGTAT GGTACAAAGA	rb	51	TGAGAGGCTG CTGCAAGAAG AATCTGGAAT CGACCTCGCG GACTCGAAC	rb	101	AGAGGCTGAG CATCCAGCGC GTGCGCGAGG AGGACGGGG CCGCTATCTG	rb	151	TGCAGGTGT GCAAACGCCAA GGGCTGGTC AACTCCCTCTG CCAGCGTGGC	rb	201	TGTGGAGGC GCCGAAGATA GAGGCAGCAT GGAGATCGTG ATCCTCGTGG
bo	1	CGGTGCCAG TGGCTGGAC GCACGTACCC AGCATCGTGT GGTACAAAGA	bo	51	TGAGAGGCTG CTGCAAGAAG AGTCCCGAAT CGACCTGGCG GACTCCAACC	bo	101	AGAAGCTGAG CATCCAGCGC GTGCGCGAGG AGGATGGGG ACGCTATCTG	bo	151	TGCAGGTGT GCAAACGCCAA GGGCTGGTC AACTCCCTCTG CCAGCGTGGC	bo	201	TGTGGAGGC TCTGAGGATA AAGGCAGCAT AGGGCAGCAT GGAGATCGTG ATCCTCGTGG
hu	1	CAGTGCTGG TGGCGGAGC GCACGGGCC AGCATCGTGT GGTACAAAGA	hu	51	CGAGAGGCTC CTGGAGAAAG AGTCCGGAAAT CGACCTGGCGA GACTCCAATIC	hu	101	AGAAGCTGAG CATCCAGCGC GTGCGCGAGG AGGACGGGG CCGCTATCTG	hu	151	TGCAGGTGT GCAAACGCCAA GGGCTGGTC AACTCCCTCTG CCAGCGTGGC	hu	201	TGTGGAGGC TCTGAGGATA AAGGCAGCAT AGGGCAGCAT GGAGATCGTG ATCCTCGTGG
mo	1	CGATGCCGG TGGCTGGAGC GCATGTGCC AGTATTGTT GGTACAAAGA	mo	51	TGAGAGGCTC CTGGAGAAAG AGTCCGGAAAT CGACCTGGCGA GACTCCAATIC	mo	101	AGAAGCTGAG CATCCAGCGC GTGCGCGAGG AGGACGGGG CCGCTATCTG	mo	151	TGCAGGTGT GCAAACGCCAA GGGCTGGTC AACTCCCTCTG CCAGCGTGGC	mo	201	TGTGGAGGC TCTGAGGATA AAGGCAGCAT AGGGCAGCAT GGAGATCGTG ATCCTCGTGG

FIG. 21A

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251	rb	GCACCGGGGT	CATTGCCGTG	TTCTTTTGGG	TCCTCCTCCCT	GCTCATCTTC
251	bo	GCACCGGGAGT	CATCGCTGTC	TTTTTCTGGG	TCCTCCTTCT	CCTICATCTTC
251	hu	GTACCCGGGT	CATCGCTGTC	TTCTTCTGGG	TCCTCCTCCCT	GCTCATCTTC
251	mo	GCACCGGGGT	CATCGCAAGT	TTCTTCTGGG	TCCTCCTCCCT	GCTCATCTTC
301	rb	TGTAACATGA	GGAGGCCAGC	CCACGGGGAC	ATCAAGACGG	GCTACTTTGTC
301	bo	TGTAACATGA	GGAGGCCAAC	CCATGCAGAC	ATCAAGACTG	GCTACTTTGTC
301	hu	TGTAACATGA	GGAGGCCGGC	CCACGGAGAC	ATCAAGACGG	GCTACCTGTC
301	mo	TGTAACATGA	AAAGGCCCTGC	CCATGCAGAC	ATCAAGACGG	GCTACCTGTC
351	rb	CATCATCATG	GATCCCCGGG	AGGTGCCCT	GGAGGAGCAA	TGTGAATAAC
351	bo	CATCATCATG	GACCCCCGGG	AGGTGCCCTT	GGAGGAGCAG	TGTGAATAAC
351	hu	CATCATCATG	GACCCCCGGG	AGGTGCCCT	GGAGGAGCAA	TGGGAATAAC
351	mo	CATCATCATG	GACCCCCGGG	AGGTGCCCTT	GGAGGAGCAG	TGTGAATAAC
401	rb	TGTCCCTACGA	CGCCAGCCAG			
401	bo	TGTCCCTACGA	TGCTAGTC			
401	hu	TGTCCCTACGA	TGCCAGCCAG			
401	mo	TGTCCCTATGA	CGCCAGCCAG			

FIG. 21B

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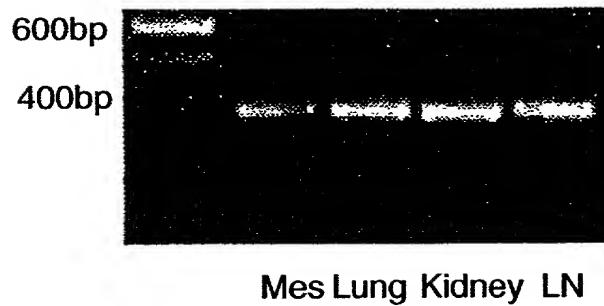
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U.S. PATENT AND TRADEMARK OFFICE
JULY 1998

rb	1	RCAVAGAHVP	SIVWVKDERL	LEEESGIDLA	DSNQRLSIQR	VREEEDAGRVL
bo	1	RCPVAGTHVP	SIVWVKDEKL	LEEESGIDLA	DSNQRLSIQR	VREEEDAGHVL
hu	1	QCLVAGAHAP	SIVWVKDERL	LEEKSGVDLA	DSNQKLSIQR	VREEEDAGRVL
mo	1	RCPVAGAHVP	SIVWVKDERL	LEKEESGIDLA	DSNQRLSIQR	VREEEDAGRVL
rb	51	CSVCKNAKGCV	NSSASAVAVGG	AEDRGSMETIV	ILVGTGVIAV	FFWVLLLLIF
bo	51	CSVCKNAKGCV	NSSASAVAVEG	SEDKGSMEIV	ILVGTGVIAV	FFWVLLLLIF
hu	51	CSVCKNAKGCV	NSSASAVAVEG	SEDKGSMEIV	ILVGTGVIAV	FFWVLLLLIF
mo	51	CSVCKNAKGCV	NSSASAVAVEG	SEDKGSMEIV	ILGIGGVIAV	FFWVLLLLIF
rb	101	CNMRRPAAHAD	IKTGVLISIM	DPGEVPLEEQ	CEVLSYDASQ	
bo	101	CNMRRPTHAD	IKTGVLISIM	DPGEVPLEEQ	CEVLSYDASQ	
hu	101	CNMRRPAAHAD	IKTGVLISIM	DPGEVPLEEQ	CEVLSYDASQ	
mo	101	CNMRRPAAHAD	IKTGVLISIM	DPGEVPLEEQ	CEVLSYDASQ	

FIG. 22A

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Mes Lung Kidney LN

FIG. 22B

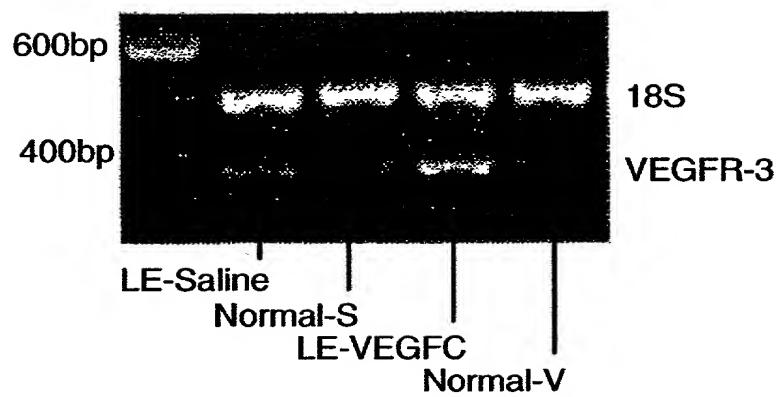


FIG. 22C

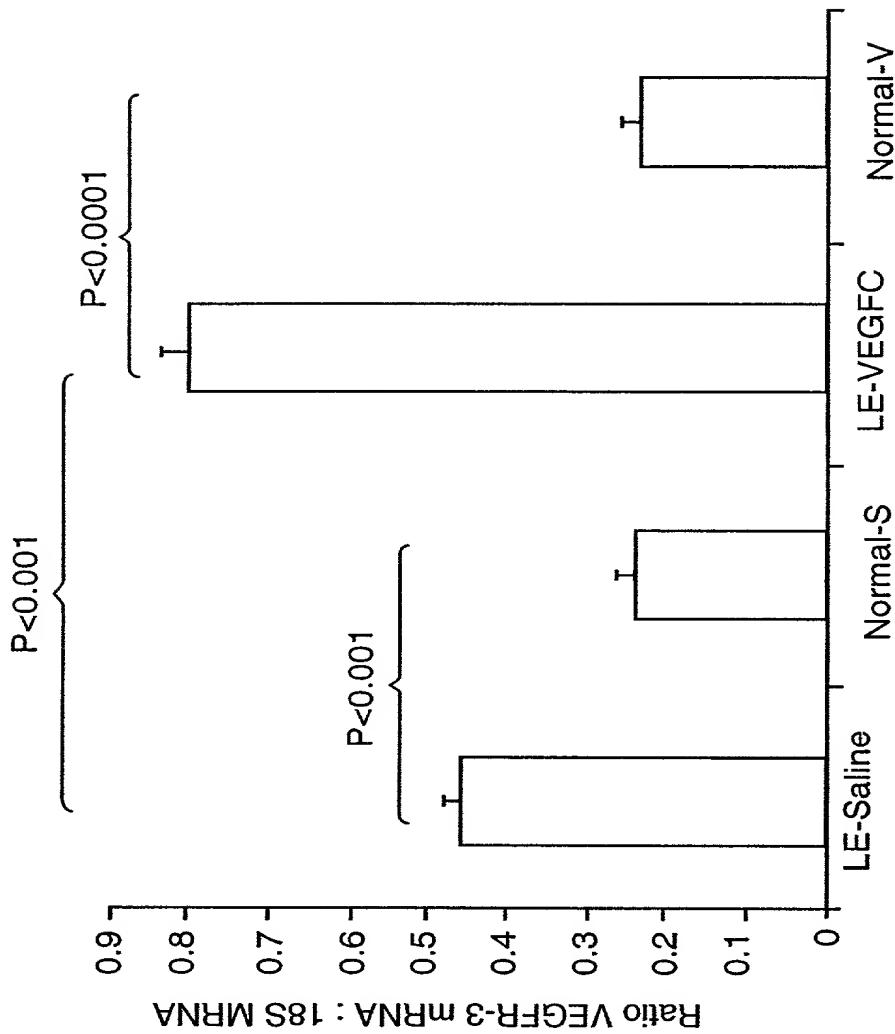


FIG. 22D

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To Treat Lymphatic Disorders
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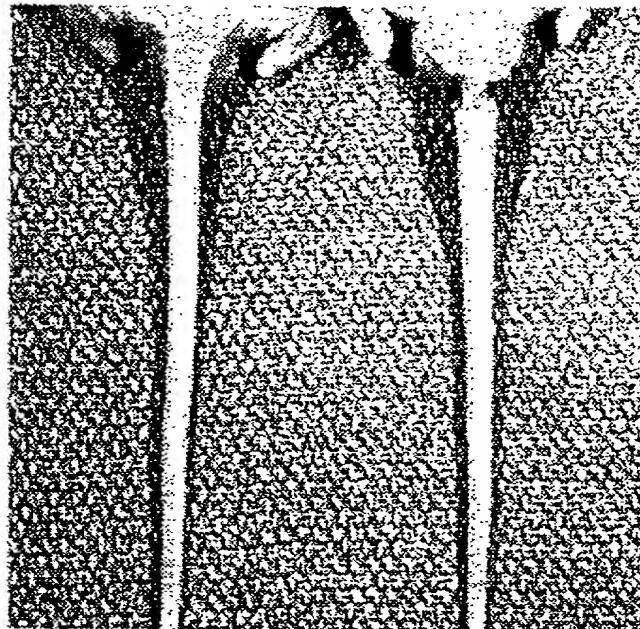


FIG. 23A

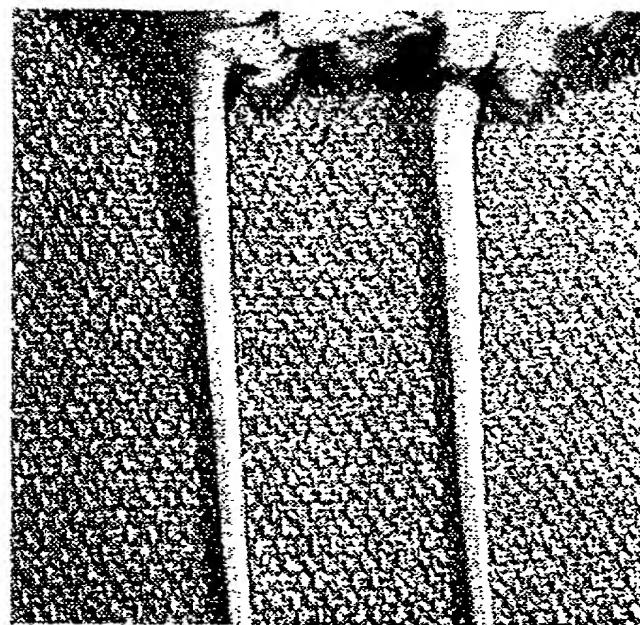


FIG. 23B

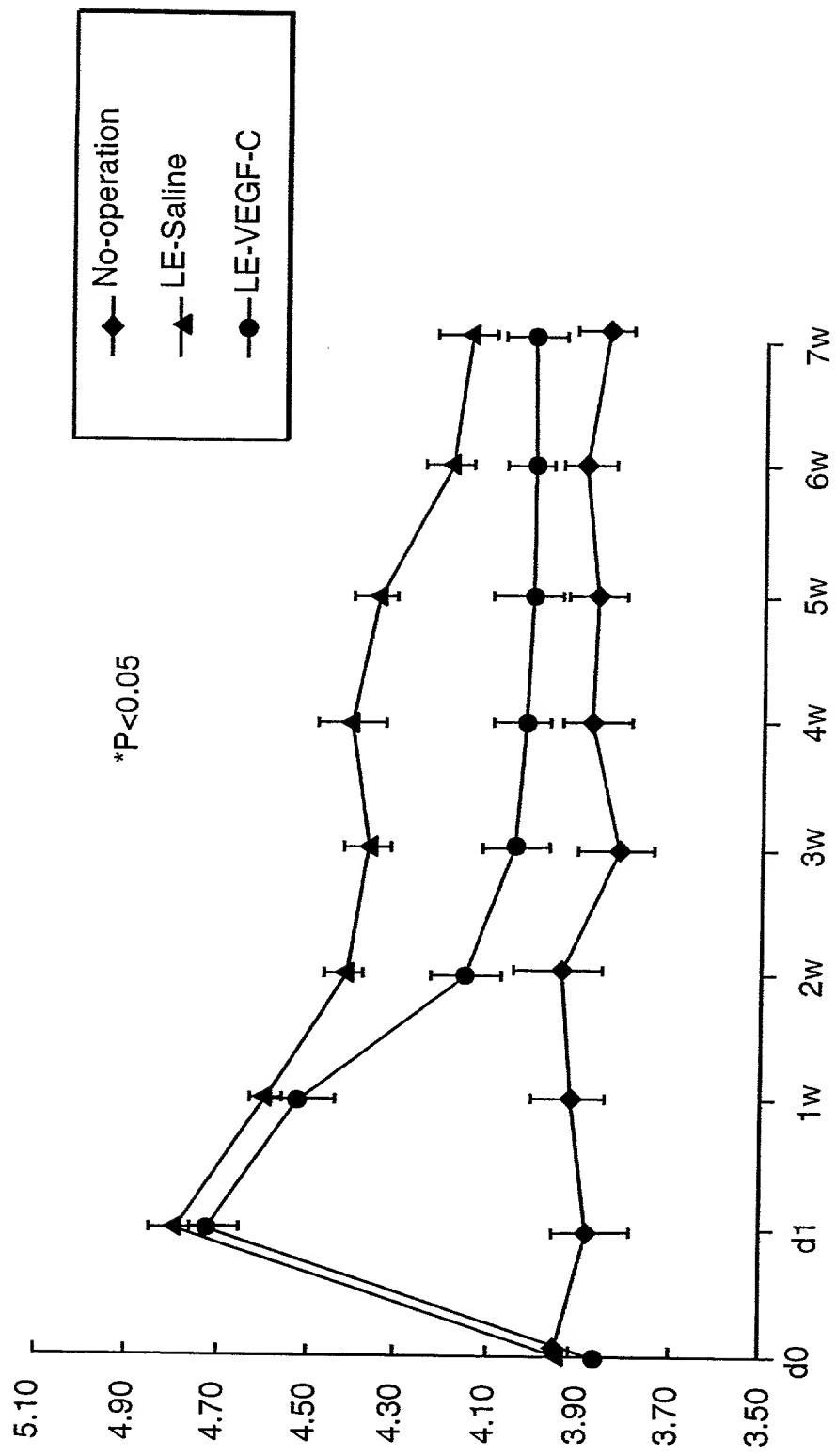


FIG. 23C

FIG. 24B

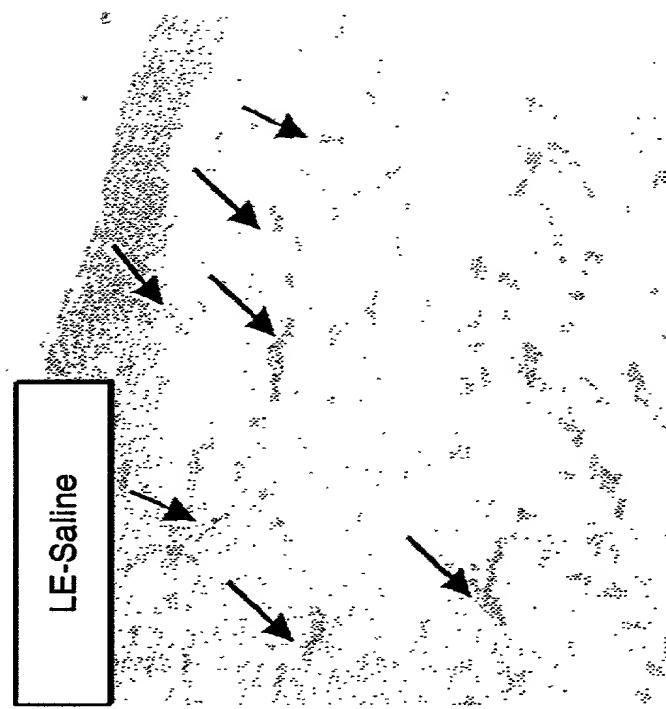
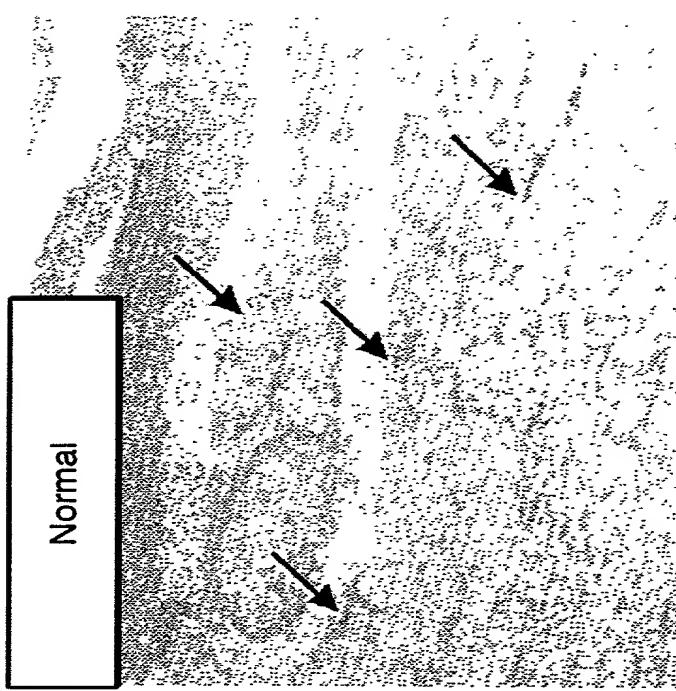


FIG. 24A



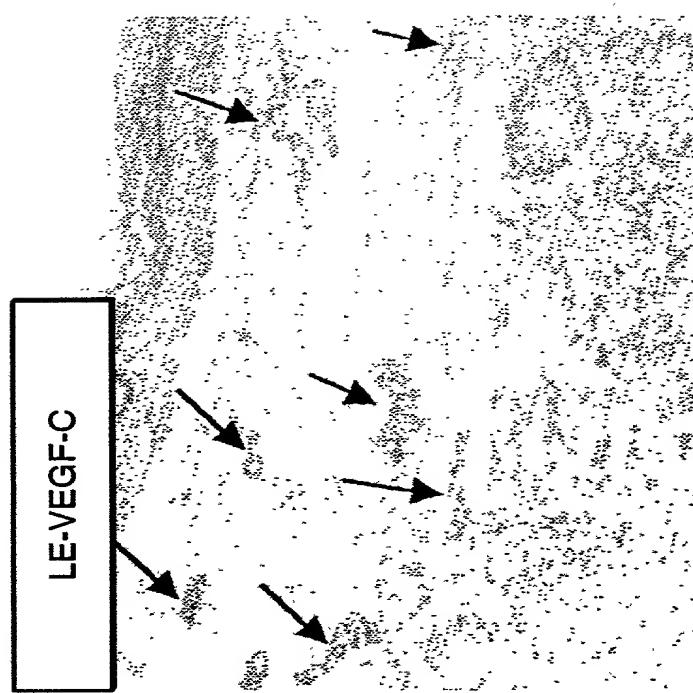


FIG. 24C

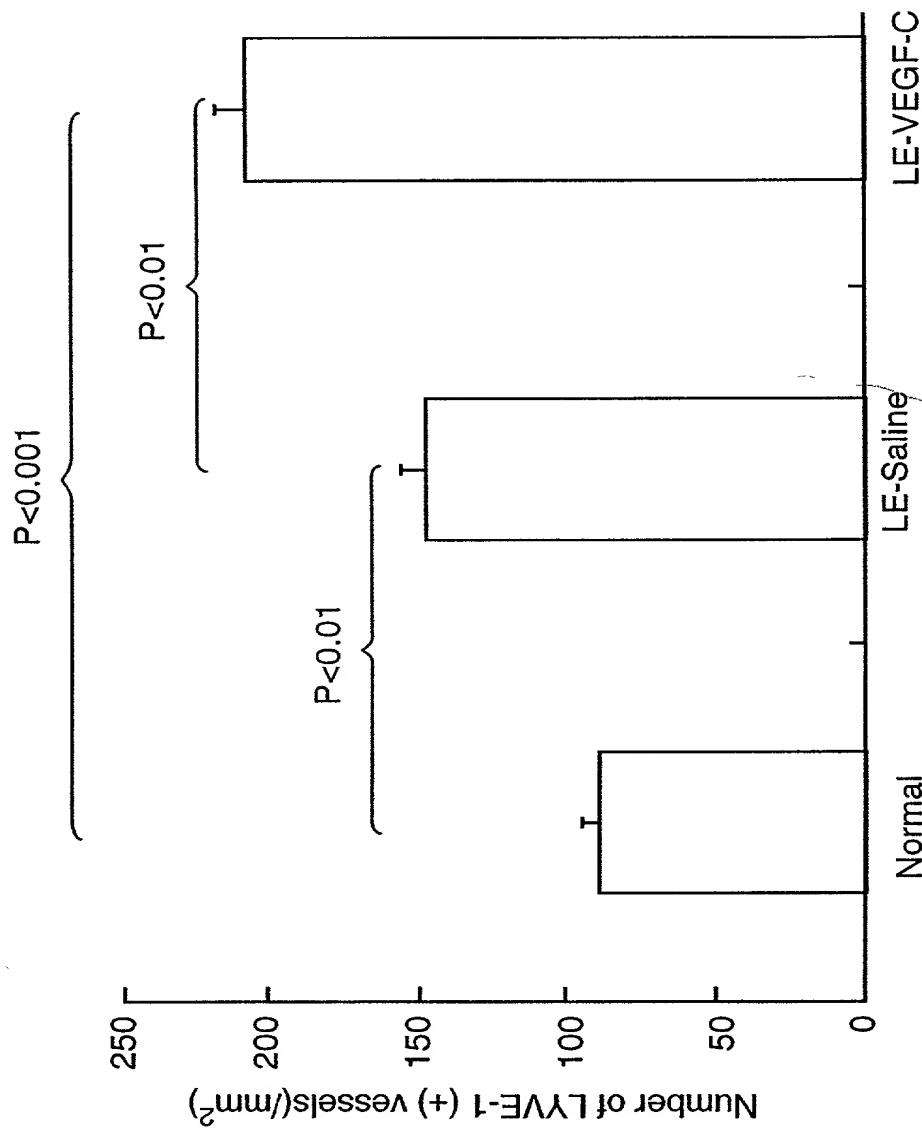


FIG. 24D